Chapter 1

Introduction

1.1 Background

Malaria is one of the world's most important health threats, especially in tropical and subtropical areas where it causes major morbidity and mortality (Kogan & Kogan, 2020). *Plasmodium falciparum* is the most virulent of the five *Plasmodium* species that infect humans, accounting for the vast majority of malaria deaths. Current treatment options rely mainly on antimalarial medications, but the fast rise of drug-resistant *P. falciparum* strains has severely restricted their efficacy. To effectively battle malaria, fresh drug candidates must be discovered quickly due to the increasing resistance (Sato, 2021).

Dihydrofolate reductase (DHFR) is a critical enzyme in *P. falciparum* that is involved in folate biosynthesis, which is required for DNA synthesis and cell replication. Inhibition of DHFR disturbs this process, eventually resulting in parasite death. DHFR inhibitors such as pyrimethamine and cycloguanil have long been utilized as antimalarial medicines (Oranusi *et al*., 2024). However, changes in the dhfr gene have resulted in widespread resistance, limiting the effectiveness of these medications. As a result, developing novel DHFR inhibitors capable of overcoming resistance is an important priority in malaria treatment development (Shibeshi *et al*., 2020).

Computational techniques to drug development have grown increasingly helpful, providing cost-effective and time-efficient tools for screening new drug candidates. Prior to experimental validation, researchers can use in silico approaches like as molecular docking, molecular dynamics simulations, and pharmacokinetic modeling to predict the binding affinity, stability, and drug-likeness of candidate compounds. This project will use these approaches to find novel drugs with strong inhibitory effects on *P. falciparum* DHFR.

This study aims to investigate the drug repurposing, especially finding the potential DHFR inhibitors, using the synthetic compound that was taken from DrugBank, therefore contributing to the continuous hunt for new antimalarial medications. The results might give a basis for next experimental validation, so enabling the creation of possibly more successful malaria medicines.

1.2 Objective

The goal of this study is to use computational techniques to find possible inhibitors of *Plasmodium falciparum* dihydrofolate reductase (DHFR). To do this, the 3D structure of *P. falciparum* DHFR will be retrieved from accessible databases and evaluated for appropriateness as a therapeutic target. Various bioactive chemicals will next be tested using molecular docking to determine their binding affinity and interactions with the enzyme. The most promising candidates will be further assessed by comparing their binding efficacy to that of existing DHFR inhibitors. The study's goal using this approach is to uncover novel chemicals that could be used as possible malaria therapy drugs.

1.3 Hypothesis

It can be hypothesized that the certain bioactive substances are expected to have a high binding affinity for *Plasmodium falciparum* dihydrofolate reductase (DHFR), comparable to or greater than known DHFR inhibitors. These chemicals are likely to generate persistent contacts with the enzyme's active site, potentially overcoming the drug resistance mechanisms found in *P. falciparum.* This study anticipates that using in silico computational approaches, molecular docking and simulation analysis will uncover viable DHFR inhibitors that could serve as lead candidates for future drug development.